The Use of Pulsed Radio Frequency Energy Therapy in Treating Lower Extremity Wounds: Results of a Retrospective Study of a Wound Registry

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Abstract
Pulsed radio frequency energy (PRFE) has been shown to stimulate cultured epidermal cells in vitro, inciting a cascade of cytokines, cyclins, growth factors, and other gene products associated with wound healing. A retrospective, descriptive study was conducted to evaluate the effect of PRFE on healing lower extremity wounds. Using data from a patient registry of 510 wounds in 413 patients, information was abstracted on patients with lower extremity wounds treated with PRFE for at least 4 weeks between 2005 and 2008 and who were evaluated 4 weeks after the start of treatment; wound size reduction was calculated. Patients with peripheral vascular disease, renal disease, poor glucose control, immune-compromise, large or deep wounds were not excluded. Of the 128 wounds (in 113 patients) that met the eligibility criteria, 35 were diabetic foot ulcers (DFUs), 42 were venous leg ulcers (VLUs), 34 were Stage II to Stage IV pressure ulcers (PUs), and 27 were other types of chronic wounds. Most patients were men (91%), receiving outpatient care (70%), and elderly (mean age 67 ± 11 years, median 64, range 41–89). Mean wound duration before starting PRFE was 29 ± 86 months (median 10, range 1–756). Mean percent reduction in wound area after 4 weeks was 49% ± 6% for pressure (P <0.0001), 38% ± 6% for diabetic (P <0.0001), 44% ± 5% for venous (P <0.0001), and 39% ± 9% for wounds of various other etiologies (P = 0.0001). The median wound reduction rate was 0.08 cm²/day (range -4.14–2.21). A considerable percentage of wounds reached >50% reduction in size at 4 weeks (DFU 40%, VLU 43%, PU 59%), suggesting that a large proportion of these PRFE-treated wounds would have healed with ongoing therapy. Additional studies to evaluate the safety, effectiveness, and efficacy of this treatment modality in the management of chronic wounds are warranted.

Key Words: retrospective descriptive study, wounds, wound registry, pulsed radio frequency energy, percent area wound reduction

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Potential Conflicts of Interest: Dr. Driver and Dr. Armstrong stated they have nothing to disclose. Dr. Frykberg is a consultant/paid advisory board member, Dr. Isenberg is an employee, and Dr. Lavery provided data analysis and manuscript preparation for Regenesis Biomedical, Inc., Scottsdale, AZ.

Chronic lower extremity wounds pose a major problem for healthcare providers and patients. They place the patient at risk for deep infection and sepsis and are frequently associated with a high degree of morbidity, mortality, and impaired quality of life. In persons with diabetes mellitus (DM), foot and leg wounds are the most common precipitating event leading to lower extremity amputation.¹ In the growing US population of people with DM, the lifetime risk of foot ulceration is 15% to 25%²; 7% to 20% of these lesions will subsequently require amputation.¹ Results of a retrospective
chart-review study have shown that lower extremity amputation is associated with a 5-year survival of 40% overall and 25% in the elderly. Venous ulcers and pressure ulcers occurring in people without DM also may cause considerable morbidity.

In a recent review of biomedical device therapeutics in wound healing, Rizzi et al suggest that advanced therapies to heal chronic wounds may provide an opportunity to reduce morbidity and mortality. One such therapy is pulsed radio frequency energy (PRFE), which has been shown to stimulate cultured epidermal cells in vitro, inciting a cascade of cytokines, cyclins, growth factors, and other gene products associated with wound healing. The use of PRFE to stimulate cell activity in chronic wounds is gaining attention. Its potential clinical utility has been reported in a recent series of case studies in the treatment of a variety of dermal ulcers. PRFE has been used to improve wound healing for several decades. In 1964, Cameron studied postoperative wound healing in a randomized controlled study of 100 general surgical patients and found accelerated healing and shortened hospital stays. In 1981, Goldin reported accelerated healing in a 67-patient randomized controlled study of skin graft patients treated pre- and postoperatively with PRFE. Improved healing outcomes were reported in the 1990s in randomized, controlled studies and case series of pressure ulcers treated with PRFE. In a 1991 randomized controlled trial (RCT), Muirhead reported accelerated healing among young women with pre-tibial lacerations.

Provant® Therapy System (Regenesis Biomedical Inc, Scottsdale, AZ) is a device that emits a nonthermal, nonionizing radio frequency signal with a carrier frequency of 27.12 MHz from a flat spiral antenna placed adjacent to the wound (see Figure 1). The device delivers a 42-µsec pulse delivered 1,000 times per second and generates an electromagnetic field thought to be responsible for the therapeutic effect. The electromagnetic field is continuously monitored and regulated to ensure consistent dosing. Waveform, energy, and treatment parameters were optimized in in vitro cell growth studies involving dermal fibroblasts and epithelial cells. PRFE delivered via this device is FDA-cleared for adjunctive treatment of postoperative pain and edema in superficial soft tissue and is currently under investigation in trials intended to demonstrate effectiveness in wound healing.

The purpose of this retrospective, descriptive study was to evaluate the effect of using PRFE on healing chronic lower extremity wounds.

Methods and Procedures

Data set: wound registry. The registry, established and maintained by Regenesis Biomedical, Inc. (Scottsdale, AZ) contains data collected by clinicians during the course of normal clinical care at 100 geographically diverse US medical facilities — 41 wound clinics, 25 skilled nursing facilities, 21 long-term acute care hospitals, eight nursing homes, five spinal cord injury units, and three other types of facilities. Four facilities have more than one type of medical care setting that submitted patient information to the registry. The registry includes data acquired serially on 413 patients with 510 wounds treated with the PRFE system from 2005 through 2008. All clinicians submitting data to the registry had been trained on proper use of the device according to the manufacturer’s instructions. Clinicians submitted case data on one to six consecutive patients, which represented their initial experience with the PRFE system. For the most part, these were patients whose chronic wounds had failed to respond to standard care such as debridement, offloading, a moist wound healing environment, and the application of more advanced modalities such as negative pressure wound therapy (NPWT), platelet-derived growth factors, or bioengineered skin equivalents. Data entry was consecutive with no inclusion or exclusion criteria. Patients were not excluded on the basis of comorbidity, wound type, wound history, or prior medical history. The database includes information on the following variables: patient age and gender; and wound age, type, stage.

Key Points

- To evaluate outcomes of care after 4 weeks using pulsed radio frequency energy (PRFE), a retrospective analysis of 113 patient records (138 chronic wounds) was conducted.
- Almost half (46%) of all wounds exhibited a reduction in size of >50%, suggesting a healing trajectory.
- Studies including control groups are warranted to ascertain the effectiveness and efficacy of this treatment modality.
(for pressure ulcers), location, and surface area (cm²). The latter was calculated based on manual measurements of wound length (greatest measurement at 12 to 6 o’clock) and width (greatest measurement at 3 to 9 o’clock), collected weekly. Foot wounds in patients with diabetes are classified as pressure ulcers or diabetic ulcers at the discretion of the clinician.

**Wound treatment and PRFE therapy.** Patients were treated by their clinicians in accordance with the guidelines and standards of their institution. For the most part, no changes were made to ongoing wound management other than the implementation of PRFE therapy. Treatment was self-administered at home by community-based patients and administered under nursing supervision to facility-based patients. Patients were treated for 30 minutes, twice daily, by placing the treatment applicator adjacent to the dressings covering their wound in accordance with the instructions for use provided by the manufacturer.

**Data retrieval and analysis.** IRB approval was obtained for this nonsignificant risk device study in accordance with the Code of Federal Regulations 21CFR 812.3. Because this was a retrospective study of existing data collected during the course of routine medical practice, informed consent requirements were waived. All data were de-identified per HIPAA regulations before submission to the registry.

A review of the data set suggested that the 4-week time point provided the most complete set of data contained in the registry; patients often missed early and/or subsequent follow-up time points. Thus, for the purpose of this study, only data of patients with lower extremity wounds that were at least 4 weeks old, were treated for at least 4 weeks with PRFE, and had data available for analysis at the 4-week follow-up visit were retrieved and included in the analysis subset. Wounds treated for less than 4 weeks, regardless of outcome, were excluded, as were all wounds without 4-week follow-up visit data, regardless of treatment duration. For the purposes of this analysis, limb wounds located distal to the acetabulofemoral joint were considered lower extremity ulcers.

Descriptive statistics were used to summarize demographic data. The number of patients reported is the number of unique patients, although a patient could contribute more than one wound to the study.

### Table 1. Patient and wound demographics

<table>
<thead>
<tr>
<th>Analysis subset demographics by wound type</th>
<th>Diabetic</th>
<th>Pressure</th>
<th>Venous</th>
<th>Other</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of wounds</td>
<td>35</td>
<td>34</td>
<td>42</td>
<td>27</td>
<td>138</td>
</tr>
<tr>
<td>Number of patients</td>
<td>33</td>
<td>28</td>
<td>32</td>
<td>24</td>
<td>113</td>
</tr>
<tr>
<td>Patient age (years)</td>
<td>63 ± 8 (62)</td>
<td>71 ± 14 (73)</td>
<td>71 ± 12 (72)</td>
<td>65 ± 9 (62)</td>
<td>67 ± 11 (64)</td>
</tr>
<tr>
<td>Site of care</td>
<td>Wound clinic 30 (91%)</td>
<td>Other settings 6 (21%)</td>
<td>25 (78%)</td>
<td>20 (83%)</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>Initial wound age (months)</td>
<td>22 ± 24 (13)</td>
<td>9 ± 10 (5)</td>
<td>45 ± 99 (11)</td>
<td>43 ± 145 (6)</td>
<td>29 ± 86 (10)</td>
</tr>
<tr>
<td>Initial wound surface area (cm²)</td>
<td>6.8 ± 9.1 (3.0)</td>
<td>15.0 ± 24.4 (6.0)</td>
<td>40.0 ± 59.0 (12.0)</td>
<td>18.1 ± 27.0 (8.6)</td>
<td>18.1 ± 27.0 (8.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number (%) of wounds per patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>94 (83%)</td>
<td>15 (13%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Percent male patients</td>
<td>91%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| a Some patients had wounds of more than one type |
| b Mean + SD (Median), Range     |
| c n (%)                         |

<table>
<thead>
<tr>
<th>Table 2. Distribution by wound type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound type</td>
</tr>
<tr>
<td>Diabetic foot ulcer</td>
</tr>
<tr>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Pressure ulcer</td>
</tr>
<tr>
<td>Not Staged</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Surgical</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Arterial</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
Healing was evaluated by analyzing percent reduction in wound surface area calculated as follows: \((1 - \frac{\text{initial wound area} - \text{final wound area}}{\text{initial wound area}}) \times 100\%\). Wound healing trajectory was defined as: \(\frac{\text{initial wound area} - \text{final wound area}}{\text{number of days of treatment}}\).

Because some patients had more than one wound, percent reduction in wound area was analyzed using repeated measures analysis of variance.

Results

Of the 413 patients in the registry, 113 patients (27%) with 138 wounds met the inclusion criteria for this study. These patients received care at 52 medical facilities; 70% of wounds were in ambulatory patients treated in outpatient wound clinics. Patients ranged in age from 41 to 89 years (see Table 1). The majority (91%) were male. Overall median wound age was 10 months (range 1 to 756 months). Of the 138 wounds, 35 were classified as diabetic ulcers, 42 were venous ulcers, 34 were pressure ulcers, and 27 were of other origin (see Table 2). Among the pressure ulcers, 10 were Stage II, six were Stage III, 12 were Stage IV, and six were not staged or deemed unstageable (see Table 1). Most diabetic and pressure ulcers were located on the foot; whereas, all venous ulcers involved the leg.

Wounds ranged widely in terms of initial surface area. Half of all wounds had an initial area >7.6 cm². Venous leg ulcers were the largest in the subset, with a median area of 12.0 cm² (see Table 1). The overall mean percent wound area reduction (PWAR) for the population at 4 weeks of therapy was 41% ± 5 (\(P < 0.0001\)). Median PWAR for the population was 45%. Overall, 46% of wounds reduced >50% in size after 4 weeks.

A somewhat higher percentage of pressure ulcers (59%) reached 50% PWAR at 4 weeks, compared to 40% and 43%, respectively, for diabetic and venous ulcers (see Table 3, Figure 2).

A few of the wounds in each category increased in size as indicated by negative wound healing trajectories. The mean wound healing trajectory for the overall population was -0.27 cm²/day ± 0.63; median was -0.08 cm²/day.

Discussion

Calculating changes in PWAR is a practical approach to assessing wound response to care. Post hoc analysis of RCT data has demonstrated that wound area reduction at 1 and 4 weeks of therapy is a robust predictor of complete wound healing. For instance, Lavery et al evaluated PWAR in a post hoc analysis of RCT data from a study assessing NPWT in patients with diabetes and foot amputation wounds. Change in wound area of at least 15% at 1 week and 60% at 4 weeks was strongly associated with complete wound healing at 16 weeks in persons that received either NPWT or control. Likewise, Sheehan et al evaluated data from a study of oxidized regenerated cellulose with collagen dressing in a 12-week RCT of patients with diabetic foot ulcers. The overall median wound area reduction at 4 weeks was 53%. Among patients with wound area reduction of 53% or more at 4 weeks, 58% eventually healed; however, in patients with less than this benchmark, only 9% healed (\(P < 0.01\)).

The use of PWAR as a measure to “predict” healing — thereby avoiding long-term use of ineffective treatments — has been established for various types of wounds and may be a useful surrogate end-point in clinical studies. The results of the current study are comparable to the outcomes reported in prospective clinical studies using more stringent exclusion criteria.
criteria for patients with comorbid conditions and suggest that a high proportion of wounds would have healed using the PRFE treatment modality. It is worth noting that most RCTs exclude patients with risk factors for poor healing such as poor glucose control, large and deep wounds, and persons who are immune-compromised. The PRFE registry did not exclude the latter high-risk patients, and as such represents a more “real-world” population.

In this analysis of lower extremity wounds, diabetic wounds decreased in surface area by a mean of 38% ± 6% and a median of 42% in 4 weeks, somewhat less than the mean P WAR among wounds that healed in the Sheehan analysis. Nonetheless, 40% of diabetic wounds reached Sheehan’s surrogate endpoint of ~50% PWAR at 4 weeks, suggesting that a large percentage of these wounds would likely heal within 12 weeks with PRFE.

The median reduction in venous ulcer surface area at 4 weeks with PRFE (44%, mean 44% ± 5%) was comparable to the median PWAR of 58% reported by Gelfand30 for venous ulcers that healed by 24 weeks in his retrospective study of 29,189 patients. In that study, wounds that reached 28.8% PWAR in 4 weeks had a positive predictive value of healing at 24 weeks of 0.80 and a negative predictive value was 0.52. In the PRFE registry, 43% of venous ulcers demonstrated a 50% PWAR (an extent of healing considerably greater than the cutoff point) at 4 weeks, suggesting that a large proportion of venous ulcers would be expected to heal within 24 weeks with the PRFE therapy.

Lundeberg31 evaluated the use of electrical stimulation in 64 patients with venous ulcers in a 12-week randomized clinical trial. At the end of the study, the average PWAR was 61% in patients in the active and 41% in the placebo arm of the study. In a similar study, Stiller32 reported an average PWAR of 47% PWAR in the active therapy group compared to a 49% increase in wound area in the sham therapy group.

For pressure ulcers, the mean PWAR in the PRFE registry was 49% ± 6% (median 58%). Feedar33 evaluated 47 patients with 67 Stage II through Stage IV pressure ulcers for 4 weeks. The mean PWAR in the control arm of the study was 34% and the active treatment arm (electrical stimulation) was 56%.

This analysis examined only those lower extremity wounds that had data available at 4 weeks of PRFE therapy and excluded all other wounds in the registry. Overall, 138 out of 254 (54%) of the total lower extremity wound population was included in the analysis. An analysis of the population of excluded wounds revealed no significant differences when compared to included wounds in terms of patient demographics, initial wound age, wound type, site of care, or the outcome parameters of PWAR, 50% PWAR, and wound healing trajectory. It is worth noting that this analysis also excluded seven wounds that had completely healed before 4 weeks. As such, the findings here may underestimate the true effectiveness of PRFE in advancing wound healing.

Limitations
Retrospective study designs and the use of data from any registry are subject to certain limitations. Because few eligibility criteria are defined, internal validity is minimized and external validity is maximized. Proper and careful statistical methodologies to control potential sources of bias that threaten internal validity were taken, yet can be considered a weakness compared to the standard RCT.34,35 Data were collected from multiple centers that use a variety of operational definitions, adjunctive wound therapies, and tools and techniques to measure the size and determine the severity of wounds. Potential confounding variables such as adherence with therapy, presence of peripheral arterial occlusive disease or other patient comorbidities, and wound depth were not available and could not be used to further explore wound outcomes. Although selection bias in this registry is more likely to be in favor of more severe than less severe wounds, the 4-week outcomes were close to those reported by others.

Conclusion
In this registry population of patients with lower extremity wounds, 4 weeks of PRFE treatment was associated with a marked decrease in wound size. The average decrease was close to that reported for other treatment modalities in published clinical trials. Applying the surrogate endpoint analysis recently published for diabetic and venous ulcers, these results suggest that a high proportion of PRFE-treated wounds would have reached full closure with ongoing PRFE therapy. Additional studies to evaluate the safety, effectiveness, and efficacy of this treatment modality in the management of chronic wounds are warranted.

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References


